| TRANSMITTAL LETTER | | | DOCKET NUMBER: P-PM 4953 |
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| SERIAL NO: 09/955,407 | FILING DATE: September 12, 2001 | EXAMINER: Not Yet Known | GROUP ART UNIT: 1635 |
| INVENTION: METHODS FOR IDENTIFYING A PREFERRED LIVER TRANSPLANT DONOR | | | |

TO COMMISSIONER FOR PATENTS

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C., 20231 on October 28, 2002.

By: Deborah L. Cadena
Deborah L. Cadena, Reg. No. 44,048

October 28, 2002
Date of Signature

Transmitted herewith are the following documents in connection with the above-identified application:

1. Request for Corrected Patent Application Publication (in duplicate).
2. Exhibits A and B.
3. Return postcard.



___ Please charge my Deposit Account No. 03-0370 the amount of $_____. A duplicate copy of this sheet is enclosed.

_X_ The Commissioner is hereby authorized to charge payment of any fees associated with this communication or credit any overpayment to Deposit Account No. 03-0370. A duplicate copy of this sheet is enclosed.

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Respectfully submitted,

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**USPTO CUSTOMER NO. 23601**

PATENT
Our Docket: P-PM 4953

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of:
Hugo R. Rosen

Serial No.: 09/955,407

Filed: September 12, 2001

For: METHODS FOR IDENTIFYING A PREFERRED LIVER TRANSPLANT DONOR

Group Art Unit: 1635

Examiner: Not Yet Known

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Commissioner for Patents
Washington, D.C. 20231

Sir:

**REQUEST FOR CORRECTED PATENT APPLICATION PUBLICATION**

The Applicants respectfully request a corrected patent application publication under 37 C.F.R. § 1.221(b).

The Applicants believe that publication No. US-2002-0119468-A1, published August 29, 2002, contains the following material mistakes apparent from USPTO records:

On page 8, column 2, claim 6, after "The method of claim" please delete "3" and substitute therefor "**5**".

On page 9, column 2, claim 32, please delete "TNF-o" and replace with "TNF-α".

Submitted herewith is a copy of pages 31 and 35 of the application as it was filed on September 12, 2001 (Exhibit A),

which clearly indicates the correct claims. Also enclosed is a copy of pages 8 and 9 of the publication as it was published on August 29, 2002, with corrections noted thereon (Exhibit B).

Accordingly, Applicants request that these errors be corrected in the USPTO's electronic copy of the Specification and that the USPTO publish a corrected patent application publication. It is respectfully submitted that the requirement that the request for correction be filed within two month from the date of the Patent Application Publication, August 29, 2002, has been satisfied.

No fee is deemed necessary to file this Request. If any fee is required, authorization is hereby given to charge the amount to Deposit Account No. 03-0370. A duplicate copy of this sheet is enclosed for this purpose.

Respectfully submitted,

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We claim:

1. A method of identifying a preferred liver transplant donor, comprising determining in an individual the presence or absence of a preferred genotype at a polymorphic site, said preferred genotype associated with altered activity of a tumor necrosis factor, wherein the presence of said preferred genotype indicates that said individual is a preferred liver transplant donor.

2. The method of claim 1, further comprising reporting the presence or absence of said preferred genotype.

3. The method of claim 1, wherein said preferred genotype is associated with lower activity of said tumor necrosis factor.

4. The method of claim 3, wherein said tumor necrosis factor is TNF-α.

5. The method of claim 3, wherein said preferred genotype is associated with lower levels of said tumor necrosis factor.

6. The method of claim 5, wherein said tumor necrosis factor is TNF-α.

7. The method of claim 6, wherein said preferred genotype is TNF308.1.

8. The method of claim 1, wherein said polymorphic site is in a TNF-α regulatory region.

EXHIBIT A

30. The method of claim 29, wherein said preferred genotype is TNF308.1.

31. The method of claim 25, wherein said polymorphic site is in a TNF-α regulatory region.

32. The method of claim 31, wherein said polymorphic site is in a TNF-α transcriptional regulatory region.

33. The method of claim 32, wherein said polymorphic site is in a TNF-α promoter region.

34. The method of claim 25, wherein said polymorphic site is in a TNF-α coding region.

TABLE 2-continued

Distribution of TNF-α Alleles, Mean HAI of Last Allograft Biopsy, and Number of Patients with Rejection

| TNF-β genotypes | n | HAI | rejection |
|---|---|---|---|
| TNFc | | | |
| (1,1) | 18 | 5.35 ± 1.4 | 7 |
| (1,2) | 12 | 4.45 ± 1.7 | 5 |
| (2,2) | 1 | 4 | 1 |
| NcoI | | | |
| (1,1) | 14 | 3.8 ± 1.5 | 6 |
| (1,2) | 13 | 6.7 ± 1.8 | 6 |
| (2,2) | 4 | 3.5 ± 1.7 | 1 |
| P value | | NS | NS |

[0068] In these studies, TNF genetic polymorphisms were determined in donor livers, and it was found that the presence of the less common 308.2 allele in the TNF-α promoter correlated with a more rapid, frequent and severe recurrence of hepatitis C in the recipient of a liver allograft. Patients who received donor livers with an inherited propensity for increased TNF-α production developed earlier histologic evidence of hepatitis C recurrence. Therefore, upon examination of a repertoire of polymorphic class III genes, it was found that a donor liver with an inherited susceptibility to excessive TNF-α production constitutes a risk factor for early and more severe hepatitis C recurrence. Excessive TNF-α could lead to an immunopathologic response that is ineffective in controlling HCV, allowing hepatitis C recurrence to occur more rapidly. Prior to these studies, no studies had addressed the potential contribution of a donor liver to the production of TNF-α in a liver transplant recipient and the recurrence of hepatitis C.

[0069] These results demonstrate that a donor liver having the TNF308.2 allele results in more rapid, frequent and severe recurrence of hepatitis C in a liver transplant recipient. In contrast, a liver donor having the TNF308.1 allele is results in a slower, less frequent and less severe recurrence of hepatitis C in a liver transplant recipient. Therefore, a donor liver having a TNF308.1 genotype is a preferred donor liver for transplantation into a recipient infected with HCV.

[0070] All journal articles and references provided herein, in parenthesis or otherwise, are incorporated herein by reference.

[0071] Although the invention has been described with reference to the examples provided above, it should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the claims.

We claim:

1. A method of identifying a preferred liver transplant donor, comprising determining in an individual the presence or absence of a preferred genotype at a polymorphic site, said preferred genotype associated with altered activity of a tumor necrosis factor, wherein the presence of said preferred genotype indicates that said individual is a preferred liver transplant donor.

2. The method of claim 1, further comprising reporting the presence or absence of said preferred genotype.

3. The method of claim 1, wherein said preferred genotype is associated with lower activity of said tumor necrosis factor.

4. The method of claim 3, wherein said tumor necrosis factor is TNF-α.

5. The method of claim 3, wherein said preferred genotype is associated with lower levels of said tumor necrosis factor.

6. The method of claim 5, wherein said tumor necrosis factor is TNF-α.

7. The method of claim 6, wherein said preferred genotype is TNF308.1.

8. The method of claim 1, wherein said polymorphic site is in a TNF-α regulatory region.

9. The method of claim 8, wherein said polymorphic site is in a TNF-α transcriptional regulatory region.

10. The method of claim 9, wherein said polymorphic site is in a TNF-α promoter region.

11. The method of claim 1, wherein said polymorphic site is in a TNF-α coding region.

12. The method of claim 1, wherein said liver transplant donor is identified for transplantation into a hepatitis C virus infected patient.

13. A method for selecting a preferred liver for transplantation, comprising the steps of:

(a) obtaining material from one or more potential liver donors;

(b) determining in said one or more potential liver donors the presence or absence of a preferred genotype at a polymorphic site, said preferred genotype associated with altered activity of a tumor necrosis factor; and

(c) harvesting a liver, or functional portion thereof, having a preferred genotype.

14. The method of claim 13, further comprising the step of:

(d) transplanting said liver, or functional portion thereof, into a recipient.

15. The method of claim 13, wherein said preferred genotype is associated with lower activity of said tumor necrosis factor.

16. The method of claim 15, wherein said tumor necrosis factor is TNF-α.

17. The method of claim 15, wherein said preferred genotype is associated with lower levels of said tumor necrosis factor.

18. The method of claim 17, wherein said tumor necrosis factor is TNF-α.

19. The method of claim 18, wherein said preferred genotype is TNF308.1.

20. The method of claim 13, wherein said polymorphic site is in a TNF-α regulatory region.

21. The method of claim 20, wherein said polymorphic site is in a TNF-α transcriptional regulatory region.

22. The method of claim 21, wherein said polymorphic site is in a TNF-α promoter region.

23. The method of claim 13, wherein said polymorphic site is in a TNF-α coding region.

24. The method of claim 14, wherein said recipient is infected with hepatitis C virus.

25. A method for limiting the severity of recurrence of hepatitis C in a liver transplant recipient, comprising the steps of:

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|---|---|---|
| 1 | CTRS | 4 |

Total number of pages: 4

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